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METHYLENECYCLOHEXANE ANNULATION. TOTAL SYNTHESIS OF (±)-AXAMIDE-1, (±)-AXISONITRILE-1, AND THE CORRESPONDING C-10 EPIMERS

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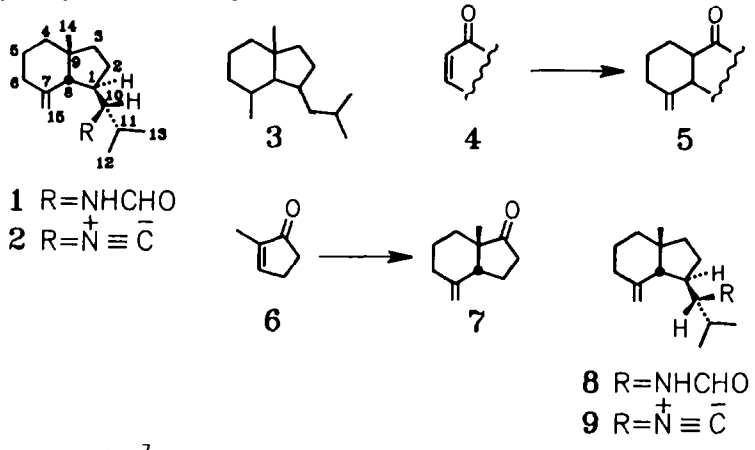
ABSTRACT - Conjugate addition of 2-(5-chloro-1-pentenyl)magnesium bromide (12) to 2-methyl-2-cyclopenten-1-one (6), followed by intramolecular alkylation of the resultant product, afforded (85%) the bicyclic ketone 7, which was transformed (77%) into the enone 16. Titanium tetrachloride-catalyzed conjugate addition of 3-methyl-1,1-bis(trimethylsiloxy)-1-butene to 16 gave (93%) a 3:2 mixture of the keto acids 20 and 21, which were separated. Compound 20, the stereochemistry of which was confirmed by a single-crystal X-ray analysis, was converted into (±)-axamide-1 (1) and (±)-axisonitrile-1 (2), while 21 was transformed into the corresponding C-10 epimers 8 and 9, respectively.

INTRODUCTION

(+)-Axamide-1 and (+)-axisonitrile-1 are structurally unusual natural products that were isolated from the marine sponge Axinella cannabina and were shown to possess the constitution[1,2] and absolute stereochemistry[3] depicted in structural formulas 1 and 2, respectively.[4,5] These interesting substances belong to the relatively small family of axane-type sesquiterpenoids, which possess the carbon skeleton 3.

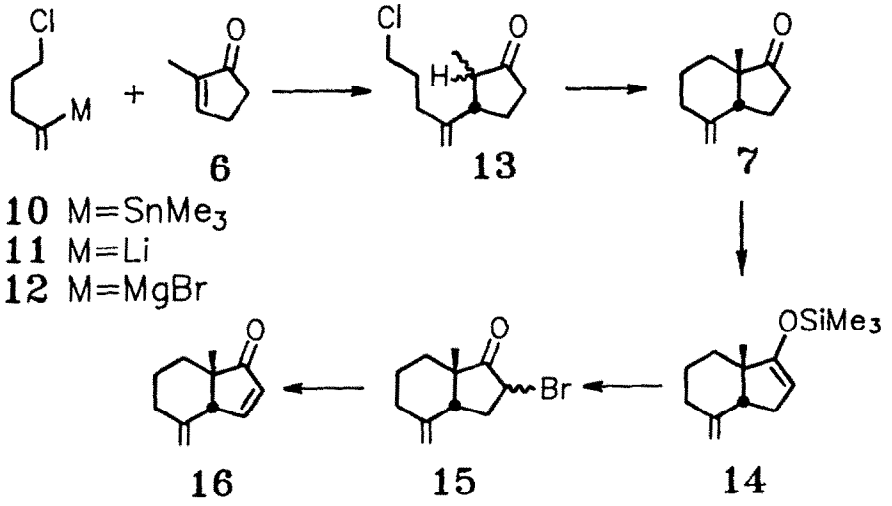


Recently, we described[7] a new methylenecyclohexane annulation sequence that can be represented in general terms by 4 → 5. When the substrate for this overall process is 2-methyl-2-cyclopenten-1-one (6), the product is the cis-fused bicyclic ketone 7.[7] It is apparent that the compound 7 could serve as a suitable precursor for a total synthesis of (±)-axamide-1 (1) and (±)-axisonitrile-1 (2). We report herein expeditious syntheses of the latter substances and of the corresponding C-10 epimers 8 and 9, respectively.[8]

RESULTS AND DISCUSSION

(a) Preparation of the enone 16. Transmetallation (MeLi, THF, -78°C) of 5-chloro-2-trimethylstannyl-1-pentene (10)[9] proceeded smoothly and the resultant vinyl-lithium 11 was readily converted, by addition of $MgBr_2$, into the Grignard reagent 12. Catalyzed (0.25 equiv. $CuBr \cdot Me_2S$, 1.0 equiv. $BF_3 \cdot Et_2O$) conjugate addition of 12 to 2-methyl-2-cyclopenten-1-one (6) provided cleanly the chloro ketone 13 (mixture of epimers). Intramolecular alkylation (KH, THF) of the latter material afforded the bicyclic ketone 7 (85% from 6). The fact that 7

possessed a cis-fused ring system was verified by a ^{1}H NMR difference NOE experiment. Thus, irradiation at δ 1.04 (Me singlet) caused enhancement of a signal at δ 2.49, which, on the basis of its chemical shift and coupling pattern (dd, J = 12, 8 Hz) was assigned to the angular proton.



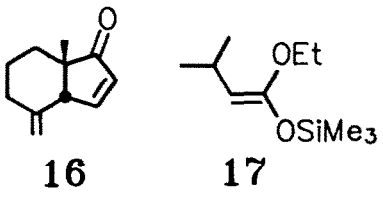
Conversion (LDA, THF; Me_3SiCl) of 7 into the enol silyl ether 14, followed by reaction of the latter material with N-bromosuccimide in dry THF,[10] gave the bromo ketone 15 (mixture of epimers). Dehydrobromination (LiBr, Li_2CO_3, DMF, heat)[11] of 15 produced the enone 16 (77% from the ketone 7).[12] Importantly, under the conditions employed for the preparation of 16 and during subsequent Lewis acid-catalyzed reactions of this substance with ketene acetals (vide infra), the exocyclic double bond showed no inclination to migrate into conjugation with the enone function. Again, the ring junction stereochemistry of 16 was confirmed by a ^{1}H NMR difference NOE experiment involving irradiation at δ 1.12 (Me group). The intensity of the angular proton signal (br s at δ 3.23) increased.

(b) Preparation of the carboxylic acids 22 and 23. An examination of molecular models makes it clear that conjugate addition of a nucleophilic species to the enone 16 would take place preferentially from the sterically more accessible top (convex) face of the molecule. In the event, $TiCl_4$-catalyzed addition[15] of (E)-1-ethoxy-3-methyl-1-trimethylsiloxy-1-butene (17) to 16 gave, in 88% yield, a mixture of two products in a ratio of ~1:1 (GLC analysis). The latter substances, 18 and 19, were subsequently shown to be stereochemically identical at C(1) (axane numbering) but, not unexpectedly, were epimeric at C(10). Use of $BF_3 \cdot Et_2O$ and $SnCl_4$ as catalysts in the Mukaiyama reaction also provided approximately equal amounts of 18 and 19. The latter substances were difficult to separate, but pure samples (18: m.p. 80-81°C; 19: m.p. 69-70°C) of each were obtained by means of column chromatography and multiple development preparative TLC.

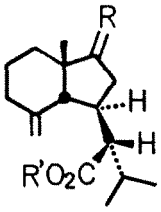
Base hydrolysis (KOH, refluxing EtOH) of a 1:1 mixture of the keto esters 18 and 19 was slow and afforded (82%) a mixture of the keto acids 20 and 21 in a ratio of about 1:2, respectively.[16] Thus, it was evident that some synthetically undesirable epimerization at C(10) had occurred during the hydrolysis reaction. Similarly, exposure of the pure keto ester 18 to N_2H_4-KOH in hot diethylene glycol (Wolff-Kishner reduction) produced (61%) the carboxylic acids 22 and 23 in a ratio of ~1:2, respectively.[16] Apparently, base-catalyzed equilibration of 18 and 19 is competitive with nucleophilic attack of hydroxide at the ester carbonyl groups. Furthermore, the major product of each of these reactions was the "undesired" epimer (21, 23, respectively).

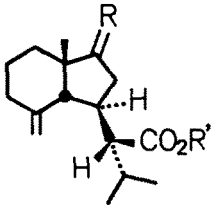
In order to avoid this unacceptable epimerization at C(10), it was necessary to prepare the keto acids 20 and 21 from 16 under reaction conditions much milder than those required for the hydrolysis of 18 and 19. To this end, the enone 16 was treated with 3-methyl-1,1-bis(trimethylsiloxy)-1-butene (24) in the presence of $TiCl_4$. Aqueous work-up provided directly, in 93% yield, a mixture of the keto acids 20 and 21 (~3:2,[16] respectively). Separation of this mixture by means of column chromatography and fractional crystallization gave the pure substances 20 (m.p. 172-173°C) and 21 (m.p. 120-121°C) in yields of 44 and 32%, respectively.

Wolff-Kishner reduction of the pure keto acids 20 and 21 afforded the corresponding carboxylic acids 22 and 23, respectively, in 90% yields. In each case, stereochemical homogeneity was maintained.

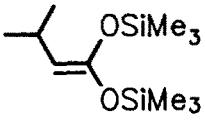


16 17





18 R=O,R'=Et **19** R=O,R'=Et
20 R=O,R'=H **21** R=O,R'=H
22 R=H_2,R'=H **23** R=H_2,R'=H



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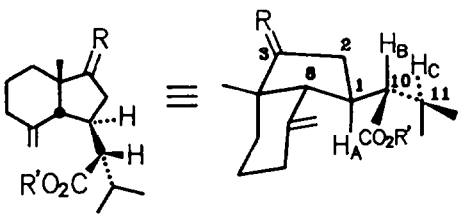
Up to this point in the synthesis, we were confident that our stereochemical assignments with respect to the chiral centers at C(1), C(8), and C(9) (axane numbering) of the intermediates 18-23 were correct. Furthermore, on the basis of the previously observed epimerizations (vide supra), it was clear that compounds 18, 20, and 22 were epimeric at C(10) with 19, 21, and 23, respectively. However, the relative stereochemistry of these substances at C(10) was uncertain.

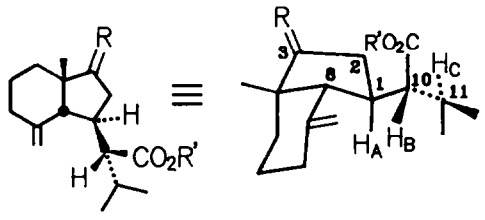
Examination of the ^1H NMR spectra of 18-23, along with conformational analyses, provided useful evidence regarding this point. Specifically, with the aid of suitable decoupling experiments, it was possible to determine the coupling constants and most of the chemical shifts associated with protons H_A, H_B, and H_C of compounds 18-23. These data, along with appropriate structural formulas, are given in Table 1. Of particular interest was the observation that the coupling constants J_{AB} and J_{BC} for the series of compounds 18, 20, and 22 are 9.5-10 Hz and 4.5-5.0 Hz, respectively, while corresponding values for the epimeric substances 19, 21, and 23 are the reverse, i.e. J_{AB} = 3.5-5.0 Hz and J_{BC} = 9.0-10 Hz.

A careful inspection of molecular models shows that the observed coupling constants can be rationalized on the basis of conformational analysis. Thus, it is reasonable to suggest that the preferred conformations for the two series of compounds (18, 20, 22 and 19, 21, 23) are those shown in Table 1. More explicitly, it is proposed that, with respect to C(1)-C(10) rotamers, the bulky isopropyl group prefers to be anti to C(8) and, in connection with rotation about the C(10)-C(11) bond, the most stable arrangement is that in which H_C is close to C(2). It seems clear that alternative staggered conformations [rotations about C(1)-C(10) and C(10)-C(11)] would be less stable than those shown in Table 1. The consequences of these (proposed) conformational preferences are that, in substances 18, 20 and 22, the H_A-H_B and H_B-H_C dihedral angles are approximately 180° and 60°, respectively, while the corresponding angles in 19, 21, and 23 are 60° and 180°, respectively. Consequently, on the basis of the Karplus equation,[17] the observed coupling constants summarized in Table 1 are certainly

Table 1. Partial ^{1}H NMR spectral data for compounds 18-23



18 R=O,R'=Et
20 R=O,R'=H
22 R=H_2,R'=H



19 R=O,R'=Et
21 R=O,R'=H
23 R=H_2,R'=H

Compound	Chemical shift[a]			Coupling constant, Hz	
	H_A	H_B	H_C	J_{AB}	J_{BC}
18	2.79-2.93(m)	2.20(dd)	1.82-1.95(m)	10.0	4.5
20	2.71-2.85(m)	2.21(dd)	1.86-2.00(m)	9.5	4.5
22	2.46-2.58(m)	2.10(dd)	?[b]	9.5	5.0
19	?[b]	2.28(dd)	1.84-2.00(m)	4.0	10.0
21	?[b]	2.32(dd)	1.86-1.99(m)	3.5	9.5
23	2.40-2.50(m)	2.18(dd)	1.96-2.08(m)	5.0	9.0

[a] In ppm from Me_4Si (δ).

[b] The precise position of these signals could not be determined.

plausible and, importantly, provided reasonable evidence to support the stereochemical assignments shown in structural formulas 18-23.

(c) X-Ray crystal structure of the keto acid 20. As indicated earlier,[5] the stereochemical portrayals for axamide-1 (1) and axisonitrile-1 (2) in the chemical literature[3,6] are not entirely unambiguous. In particular, the stereochemistry at C(10) of these substances appeared to be depicted incorrectly. Therefore, even though steric approach control considerations and the ^{1}H NMR data discussed above provided strong support for our stereochemical assignments as related to the synthetic intermediates 18-23, we wished to acquire indisputable evidence regarding this point. To this end, an X-ray analysis of the crystalline keto acid 20, m.p. 172-173°C, was undertaken.

The crystal structure of 20 consists of pairs of molecules having the absolute configurations 1(R), 8(R), 9(S), 10(S) and 1(S), 8(S), 9(R), 10(R), linked across centers of symmetry by O-H···O hydrogen bonds [O(2)-H(O)···O(3) (1-x, -y, 1-z), H···O = 1.97 (10) Å, O···O = 2.644 (5) Å, O-H···O = 113 (7)°] to form the familiar carboxylic acid dimers. The molecule (Fig. 1) contains cis-fused five- and six- membered rings, the latter having a chair conformation distorted by the sp^2-hybridized C(7) atom. Interestingly, the conformation of 20 in the crystal is very close to that initially predicted on the basis of conformational analysis and supported by the ^{1}H NMR spectral data (see Table 1). Bond lengths and angles (Tables 3 and 4, **EXPERIMENTAL** section) are generally as expected. The lengthening of the C(1)-C(8) and C(10)-C(11) bonds is probably due to intramolecular steric strain [C(16)···C(4) = 3.094(7), C(1)···C(13) = 3.089(8), C(16)···C(13) = 3.090(9), C(16)···C(12) = 2.969(8) Å].

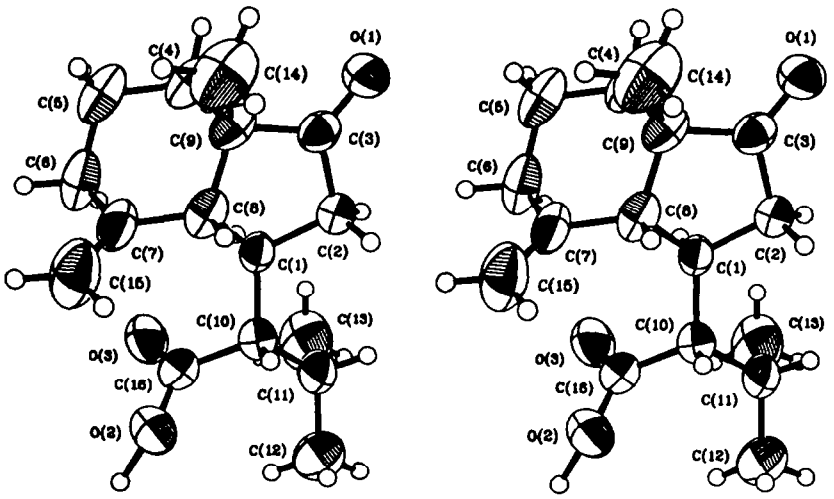
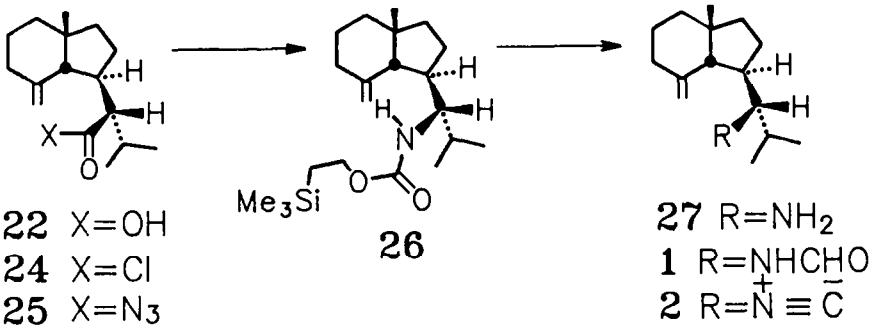


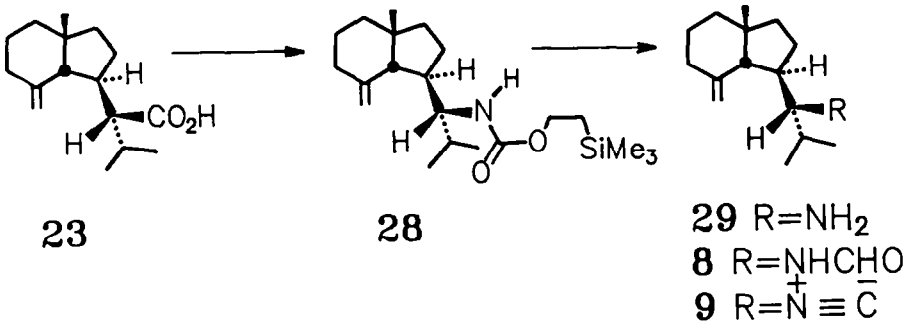
Figure 1. Stereoview of the keto acid 20; 50% probability thermal ellipsoids are shown for the non-hydrogen atoms. The 1(R), 8(R), 9(S), 10(S) enantiomer is shown.

(d) Preparation of (±)-axamide-1 (1), (±)-axisonitrile-1 (2), and the corresponding C-10 epimers 8 and 9. Conversion of the carboxylic acid 22 into the acyl azide 25, via the chloride 24, was accomplished by standard reactions. Curtius rearrangement ($PhCH_3$, 80°C) of 25, followed by reaction of the resultant isocyanate with 2-trimethylsilylethanol,[18] afforded (89% from 22) the stereochemically homogeneous carbamate 26, m.p. 79.5-80.5°C. Treatment of the latter substance with n-Bu_4NF in warm THF[18] provided the primary amine 27 (72%). Formylation (AcOCHO, ether)[19] of 27 gave (±)-axamide-1 (1) in 90% yield. The ^1H NMR spectrum of this material was rather complicated. Indeed, the appearance of two doublets due to formamide protons (δ 8.15, 0.6 H, J = 2 Hz; δ 7.90, 0.4 H, J = 12 Hz) showed that (±)-1 consisted of a mixture of cis and trans rotamers associated with the amide linkage, in a ratio of about 3:2, respectively. Unfortunately, we were not able to secure an authentic sample of natural axamide-1 and comparison of the limited spectral data reported for this substance[2] with those exhibited by our synthetic material did not lead to an unambiguous conclusion regarding compound identity. However, dehydration (p-toluenesulfonyl chloride, pyridine)[20] of (±)-1 afforded, cleanly and efficiently (86%), crystalline (±)-axisonitrile-1 (2), m.p. 45-46°C. The chromatographic behavior (GLC, TLC) and the ^1H NMR spectrum (400 MHz) of (±)-2 were found to be identical with those of a sample of (+)-axisonitrile.[21] The overall yield of (±)-2, starting from 2-methyl-2-cyclopenten-1-one (6), was nearly 13%.



Conversion of the carboxylic acid 23 into the carbamate 28 (m.p. 86-87°C, 82% overall) was accomplished via a sequence of reactions[18] identical with that employed for the transformation of 22 into 26. Fluoride promoted conversion[18] of 28 into the amine 29, followed by formylation[19] of the latter material, gave (±)-10-epi-axamide-1 (8) (64%). Again,

the ^{1}H NMR spectrum of this material exhibited two formamide protons (δ 8.31, br s, 0.5H; δ 7.97, d, J = 11 Hz, 0.5H), indicating that (±)-8 consisted of a mixture of cis and trans rotamers in a ratio of ~1:1. Dehydration[20] of (±)-8 provided (87%) crystalline (±)-10-epi-axisonitrile-1 (9), m.p. 53-54°C. The 400 MHz ^{1}H NMR spectrum of (±)-9, as well as its chromatographic behavior (GLC), were clearly different from those of natural (+)-axisonitrile-1 (2).[21]



23 **28** **29** R=NH_2 **8** R=NHCHO **9** R=$\overset{+}{N}\equiv\overset{-}{C}$

EXPERIMENTAL

General. Melting points and distillation temperatures are uncorrected. IR spectra were recorded on either a Perkin-Elmer model 710B or a Perkin-Elmer model 1710 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on $CDCl_3$ solutions. Signal positions are given in ppm (δ) relative to Me_4Si. High resolution mass spectra were recorded with a Kratos MS-50 mass spectrometer. Gas-liquid chromatography was performed on Hewlett-Packard models 5880 or 5890 gas chromatographs equipped with 12.5 m x 0.21 mm fused silica columns coated with cross-linked OV-210 (column A) or SE-54 (column B). Analytical TLC was carried out on commercial aluminum-backed silica gel plates (E. Merck, Type 5554), while preparative TLC was done with 20 cm x 20 cm plates coated with 2 mm of silica gel (E. Merck, silica gel 60). Conventional column chromatography and flash chromatography[22] were done with 70-230 and 230-400 mesh silica gel (E. Merck), respectively. Reagents and solvents were purified and dried using standard methods.

Note. All compounds for which high resolution mass measurements are given exhibited one spot on TLC analysis and/or essentially one peak on GLC analyses (columns A and/or B).

Preparation of the bicyclic ketone 7. To a cold (-78°C), stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (10)[9] (1.96 g, 7.3 mmol) in 30 mL of dry THF (under argon) was added 9.1 mmol of ethereal MeLi and the mixture was stirred for 15 min. Solid $MgBr_2 \cdot Et_2O$ (1.88 g, 7.3 mmol) was added and, after 20 min, solid $CuBr \cdot Me_2S$ (376 mg, 1.8 mmol), a solution of 2-methyl-2-cyclopenten-1-one (6) (541 mg, 5.6 mmol) in 5 mL of dry THF, and $BF_3 \cdot Et_2O$ (0.9 mL, 7.3 mmol) were added consecutively. The bright yellow mixture was stirred at -78°C for 3 h. Saturated aqueous NH_4Cl (pH 8) (25 mL) and ether (30 mL) were added and the mixture was allowed to warm to room temperature with vigorous stirring and exposure to air. The blue aqueous layer was separated and washed twice with ether. The combined organic extract was washed with saturated aqueous NH_4Cl (pH 8), dried ($MgSO_4$), and concentrated. Flash chromatography (80 g silica gel, 1:4 ether-petroleum ether) of the residue and distillation (90-95°C/0.2 Torr) of the oil thus obtained gave 996 mg (89%) of the ketone 13 (2:1 mixture of epimers). A solution of the latter material in 5 mL of dry THF was added to a stirred suspension of KH in 5 mL of dry THF (argon atmosphere) and the mixture was stirred at room temperature for 2 h. Saturated aqueous ammonium chloride (5 mL) and ether (10 mL) were added. The aqueous layer was separated and extracted twice with ether. The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated. Distillation (68-73°C/23 Torr) of the residual oil gave 789 mg (85% from 6) of the bicyclic ketone 7 as a colorless oil: IR (neat)

3050, 1730, 1635, 900 cm^{-1}; ^1H NMR (400 MHz) δ 1.04 (s, 3H), 1.18-1.27 (m, 1H), 1.43-1.56 (m, 2H), 1.60-1.72 (m, 1H), 1.83-1.95 (m, 1H), 1.98-2.12 (m, 1H), 2.12-2.28 (m, 3H), 2.43-2.55 (m, 2H), 4.76-4.83 (m, 2H). Difference NOE experiment: irradiation at δ 1.04 caused enhancement of the angular proton signal at δ 2.49 (dd, J = 12, 8 Hz). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1202; found: 164.1205.

Preparation of the enol trimethylsilyl ether 14. To a cold (-78°C), stirred solution of LDA (2.3 mmol) in 2.3 mL of dry THF (argon atmosphere) was added a solution of the ketone 7 (310 mg, 1.9 mmol) in 2 mL of dry THF. The solution was stirred at -78°C for 40 min, during which time a white solid formed. Me_3SiCl (310 μL, 2.5 mmol) was added and, after 5 min, the mixture was allowed to warm to room temperature and then was stirred for a further 90 min. During this time, the initially formed precipitate dissolved and, after a short time, was replaced by another white precipitate. The mixture was diluted with 5 mL of dry ether and then was filtered. After the filtrate had been concentrated (reduced pressure), the residue was treated with 2 mL of dry ether and the resultant mixture was filtered again. Removal of the solvent from the filtrate, followed by distillation (82-88°C/25 Torr) of the remaining liquid, provided 446 mg (99%) of the enol ether 14 as a colorless oil: IR (neat) 3050, 1630, 1252, 1235, 920, 895 cm^{-1}; ^1H NMR (400 MHz) δ 0.21 (s, 9H), 0.97 (s, 3H), 1.24-1.65 (m, 4H), 2.09-2.26 (m, 4H), 2.42 (t, 1H, J = 9 Hz), 4.48 (t, 1H, J = 2 Hz), 4.70 (br s, 2H). Exact Mass calcd. for $C_{14}H_{24}OSi$: 236.1597; found: 236.1599.

Preparation of the enone 16. A solution of NBS (355 mg, 2.0 mmol) in 6 mL of dry THF was added dropwise to a solution of the enol silyl ether 14 (446 mg, 1.9 mmol) in 3 mL of dry THF at 0°C (argon atmosphere). The mixture was stirred for 15 min and then H_2O (15 mL) and CCl_4 (15 mL) were added. The aqueous layer was separated and extracted twice with CCl_4. The combined organic extract was washed with water, dried ($MgSO_4$), and concentrated. Distillation (48-52°C/0.2 Torr) of the residue gave 425 mg (92%) of the bromo ketone 15 (85:15 mixture of epimers) as a sweet-smelling, colorless oil. A solution of this material in 5 mL of dry DMF was added to a stirred slurry of LiBr (315 mg, 3.6 mmol) and Li_2CO_3 (400 mg, 5.4 mmol) in 4 mL of dry DMF (argon atmosphere). The mixture was refluxed for 3 h and then was cooled and filtered. The collected salt was washed with ether. The combined filtrate was washed with water (3 x 15 mL), dried ($MgSO_4$), and concentrated. Distillation (90-100°C/25 Torr) of the residue provided 239 mg (78% from the enol silyl ether 14) of the enone 16 as a colorless oil: IR (neat) 3050, 3025, 1700, 1640, 900, 820 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (s, 3H), 1.34-1.58 (m, 3H), 1.65 (m, 1H), 2.09 (m, 1H), 2.22 (m, 1H), 3.23 (br s, 1H), 4.90, 4.92 (br s, br s, 1H each), 6.20 (dd, 1H, J = 5.5, 2 Hz), 7.48 (dd, 1H, J = 5.5, 2.5 Hz). In a difference NOE experiment, irradiation at δ 1.12 caused enhancement of the signal at δ 3.23 (angular proton). Exact Mass calcd. for $C_{11}H_{14}O$: 162.1045; found: 162.1046.

(E)-1-Ethoxy-3-methyl-1-trimethylsiloxy-1-butene (17). To a cold (-78°C), stirred solution of LDA (2.76 mmol) in 2.8 mL of dry THF (argon atmosphere) was added a solution of ethyl 3-methylbutanoate (299 mg, 2.3 mmol) in 2 mL of dry THF. The mixture was stirred at -78°C for 30 min and then Me_3SiCl (410 μL, 3.2 mmol) was added. The solution was allowed to warm to room temperature and then was stirred for 1.5 h. The mixture was diluted with dry ether (5 mL) and filtered. After the solvent had been removed from the filtrate (reduced pressure), the residue was treated with dry ether (2 mL) and filtration was repeated. Concentration of the filtrate and distillation (60-65°C/25 Torr) of the remaining oil provided 419 mg (90%) of the ketene acetal 17 as a colorless oil that, on the basis of a GLC analysis (column B) consisted of a mixture of (E) and (Z) isomers in a ratio of 95:5, respectively. ^1H NMR (80 MHz) δ 0.22 (s, 9H), 0.95 (d, 6H, J = 7 Hz), 1.22 (t, 3H, J = 7 Hz), 2.25-2.80 (m, 1H), 3.62 (d, 1H, J = 9 Hz), 3.82 (q, 2H, J = 7 Hz). This material was used immediately for the next reaction.

Preparation of the keto esters 18 and 19. To a cold (-78°C), stirred solution of the enone 16 (198 mg, 1.23 mmol) in 2 mL of dry CH_2Cl_2 (argon atmosphere) was added $TiCl_4$ (150 μL, 1.36 mmol) and the solution was stirred for 5 min. A solution of the ketene acetal 17 (311 mg,

1.5 mmol) in 2 mL of dry CH_2Cl_2 was added. The solution turned dark red. After the mixture had been stirred at -78°C for 2 h, it was treated with H_2O (8 mL) and then was extracted with ether (3 x 15 mL). The combined extract was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (80 g silica gel, 1:3 ether-petroleum ether) provided 322 mg (89%) of a white solid that, on the basis of a GLC analysis (column B), consisted of a 1:1 mixture of **18** and **19**. By use of a combination of column chromatography (10 g silica gel per 10 mg of mixture, slow elution with 1:10 ether-petroleum ether) and multiple development preparative TLC (11 times, 1:10 ether-petroleum ether), pure samples of the keto esters **18** and **19** were obtained.

Compound **18** exhibited m.p. 80-81°C (from petroleum ether); IR ($CHCl_3$) 3080, 3035, 1730, 1645, 1374, 1181, 902 cm^{-1}; ^1H NMR (400 MHz) δ 0.94, 0.95 (d, d, 3H each, J = 7 Hz), 1.01 (s, 3H), 1.23 (t, 3H, J = 7 Hz), 1.20-1.30 (obscured m, 1H), 1.40-1.63 (m, 2H), 1.68-1.78 (m, 1H), 1.82-1.95 (partially obscured m, 1H), 1.94 (dd, 1H, J = 18.5, 11.5 Hz), 2.07-2.15 (m, 1H), 2.15 (partially obscured d, 1H, J = 11 Hz), 2.20 (partially obscured dd, 1H, J = 10, 4.5 Hz), 2.18-2.31 (m, 1H), 2.65 (dd, 1H, J = 18.5, 7.5 Hz), 2.79-2.93 (m, 1H), 3.92-4.06 (m, 2H), 4.72 (br s, 1H), 4.77 (t, 1H, J = 2 Hz). Decoupling experiments: irradiation at δ 2.86 caused the signals at δ 1.94, 2.15, 2.20, and 2.65 to collapse to a d (J = 18.5 Hz), a s, a d (J = 4.5 Hz), and a d (J = 18.5 Hz), respectively; irradiation at δ 2.65 caused the resonance at δ 1.94 to collapse to a d (J = 11.5 Hz) and the signal at δ 2.86 to simplify; irradiation at δ 0.95 caused the multiplet at δ 1.82-1.95 to collapse to a broad, unresolved signal. Difference NOE experiment: irradiation at δ 1.01 caused a weak enhancement of the signal at δ 2.15 (d, J = 11.5 Hz). Exact Mass calcd. for $C_{18}H_{28}O_3$: 292.2039; found 292.2045.

The keto ester **19** exhibited m.p. 69-70°C (from petroleum ether); IR ($CHCl_3$) 3070, 3028, 1728, 1645, 1377, 1188, 903 cm^{-1}; ^1H NMR (400 MHz) δ 0.91, 0.95 (d, d, 3H each, J = 7 Hz), 1.03 (s, 3H), 1.27 (t, 3H, J = 7 Hz), 1.22-1.30 (obscured m, 1H), 1.45-1.55 (m, 2H), 1.67-1.77 (m, 1H), 1.84-2.00 (m, 1H), 2.03-2.17 (m, 1H), 2.30 (partially obscured d, 1H, J = 11 Hz), 2.18-2.28 (m, 1H), 2.28 (dd, 1H, J = 10, 4 Hz), 2.52 (dd, 1H, J = 17, 7 Hz), 2.56-2.74 (m, 2H), 4.16 (q, 2H, J = 7 Hz), 4.84 (t, 1H, J = 1.5 Hz), 4.94 (t, 1H, J = 2 Hz). Decoupling experiments: irradiation at δ 0.92 caused the multiplet at δ 1.84-2.00 to collapse to a d (J = 10 Hz); irradiation at δ 1.91 caused both of the doublets at δ 0.91 and 0.95 to collapse to singlets and the dd at δ 2.28 to collapse to a very broad, unresolved signal. Difference NOE experiment: irradiation at δ 1.03 caused enhancement of the signal at δ 2.30 (d, J = 11 Hz). Exact Mass calcd. for $C_{18}H_{28}O_3$: 292.2039; found: 292.2041.

3-Methyl-1,1-bis(trimethylsiloxy)-1-butene (24). To a cold (-78°C), stirred solution of LDA (1.78 mmol) in 1.8 mL of dry THF (argon atmosphere) was added 3-methylbutanoic acid (82.8 mg, 0.81 mmol) in 2 mL of dry THF. After 5 min, the solution was warmed to 0°C and then was stirred at this temperature for 1.5 h. A white precipitate formed. Dry HMPA (0.31 mL, 1.78 mmol) was added and the mixture was stirred for 15 min. During this time, the white solid dissolved. To the clear, pale yellow solution was added 0.25 mL (1.97 mmol) of Me_3SiCl and the solution was allowed to warm to room temperature. After 1.5 h, aqueous $NaHCO_3$ (5%, 10 mL) and pentane (10 mL) were added. The organic layer was separated and washed (4 x 10 mL) with 5% aqueous $NaHCO_3$, and then was dried ($MgSO_4$). Removal of the solvent and distillation (80-90°C/25 Torr) of the remaining liquid provided 172 mg (86%) of the ketene acetal **24** as a colorless oil. This material, which was used immediately for the next reaction, exhibited ^1H NMR (270 MHz) δ 0.20, 0.22 (s, s, 9H each), 0.91 (d, 6H, J = 7 Hz), 2.41 (m, 1H), 3.42 (d, 1H, J = 8 Hz).

Preparation of the keto acids **20** and **21**.

(a) By conjugate addition of the ketene acetal **24** to the enone **16**. $TiCl_4$ (69 μL, 0.63 mmol) was added to a stirred solution of the enone **16** (93 mg, 0.57 mmol) in 1 mL of dry CH_2Cl_2 at -78°C (argon atmosphere) and the solution was stirred for 5 min. To the orange-red mixture was added slowly a solution of the ketene acetal **24** (168 mg, 0.68 mol) in 1 mL of dry

CH_2Cl_2. The color of the solution turned to reddish brown. After the mixture had been stirred for 2 h at -78°C, water (10 mL) was added and the mixture was allowed to warm to room temperature and then was extracted with ether (3 x 15 mL). The combined ether extract was dried ($MgSO_4$) and concentrated to afford 150 mg of crude material that, on the basis of its ^1H NMR spectrum, consisted of a mixture of 20 and 21 in a ratio of ~3:2, respectively. Subjection of the mixture to a combination of repeated column chromatography (20 g silica gel per 100 mg of mixture, 2:3 ether-petroleum ether) and fractional crystallization from ether provided 66 mg (44%) of the keto acid 20, 48 mg (32%) of the keto acid 21, and 18 mg (12%) of a mixture of 20 and 21.

The keto acid 20 exhibited m.p. 172-173°C (from ether); IR ($CHCl_3$) 3400-2500 (br), 1735, 1703, 1646, 1375, 901 cm^{-1}; ^1H NMR (400 MHz) δ 0.93, 1.05 (d, d, 3H each, J = 7 Hz), 1.00 (s, 3H), 1.23 (br d, 1H, J = 12 Hz), 1.38-1.59 (m, 2H), 1.66-1.75 (m, 1H), 1.86-2.00 (obscured m, 1H), 1.94 (dd, 1H, J = 18.5, 11.5 Hz), 2.06-2.15 (m, 1H), 2.16 (partially obscured br d, 1H, J = 10.5 Hz), 2.21 (partially obscured dd, 1H, J = 9.5, 4.5 Hz), 2.20-2.30 (m, 1H), 2.62 (dd, 1H, J = 18.5, 7.5 Hz), 2.71-2.85 (m, 1H), 4.76 (t, 1H, J = 1.5 Hz), 4.80 (br s, 1H), 10.5-11.2 (br, 1H). Decoupling experiments: irradiation at δ 2.62 caused the signals at δ 2.71-2.85 and 1.86-2.00 to simplify; irradiation at δ 2.78 caused the signals at δ 2.62, 2.16, 2.21, and 1.94 to collapse to a d (J = 18.5 Hz), a br s, a br s, and a d (J = 18.5 Hz), respectively. Exact Mass calcd. for $C_{16}H_{24}O_3$: 264.1726; found: 264.1726.

The keto acid 21 exhibited m.p. 120-121°C (from ether-petroleum ether); IR ($CHCl_3$) 3400-2500 (br), 1733, 1703, 1646, 1376, 907 cm^{-1}; ^1H NMR (400 MHz) δ 0.95, 0.96 (d, d, 3H each, J = 6.5 Hz), 1.03 (s, 3H), 1.21-1.30 (m, 1H), 1.42-1.57 (m, 2H), 1.66-1.77 (m, 1H), 1.86-1.99 (m, 1H), 2.01-2.04 (m, 1H), 2.17-2.23 (obscured signal, 1H), 2.22 (br d, 1H, J = 10.5 Hz), 2.32 (dd, 1H, J = 9.5, 3.5 Hz), 2.46-2.70 (m, 3H), 4.88 (br s, 1H), 4.94 (t, 1H, J = 2 Hz). Decoupling experiments: irradiation at δ 1.92 caused the doublets at δ 0.95 and 0.96 to sharpen and the signal at δ 2.32 to collapse to a broad, unresolved peak; irradiation at δ 2.32 caused the signal at δ 1.86-1.99 to collapse to a septet (J = 6.5 Hz) and the resonance at δ 2.46-2.70 to simplify; irradiation at δ 0.95 caused the signal at δ 1.86-1.99 to collapse to a d (J = 9.5 Hz). Exact Mass calcd. for $C_{16}H_{24}O_3$: 264.1726; found: 264.1727.

(b) By hydrolysis of the keto esters 18 and 19. A mixture of the keto esters 18 and 19 (318 mg, 1.1 mmol, ratio ~1:1) and KOH (600 mg, 10.9 mmol) in 1.5 mL of ethanol and 0.5 mL of water was refluxed for 48 h. The cooled solution was washed with ether (2 x 5 mL) and then was acidified (1N hydrochloric acid). The mixture was extracted with ether (3 x 10 mL), and the ether extract was dried ($MgSO_4$) and concentrated. Separation of the resultant mixture as described above gave 62 mg (21%) of the keto acid 20, 146 mg (50%) of the keto acid 21, and 32 mg (11%) of a mixture of 20 and 21.

X-ray crystallographic analysis of (±)-20. A crystal bounded by the six faces (followed by distances in mm between parallel faces): {110}, 0.32, {1-10}, 0.60, and {001}, 0.07, was mounted in a general orientation. Unit-cell parameters were refined by least-squares on $2\sin\theta/\lambda$ values for 25 reflections with 2θ = 60-90° measured with CuK_α radiation ($\lambda(K_{\alpha_1})$ = 1.540562 Å). Crystal data at 22°C are: $C_{16}H_{24}O_3$, fw = 264.36, triclinic, a = 10.708(1), b = 12.472(2), c = 6.327(1) Å, α = 79.87(2), β = 78.37(1), γ = 73.23(1)°, V = 786.1(2) $Å^3$, Z = 2, D_c = 1.117 g cm^{-3}, $F(000)$ = 288, $\mu(CuK_\alpha)$ = 5.7 cm^{-1}. Absent reflections: none, space group $P\bar{1}$ (reduced cell) from structure analysis.

Intensities were measured with nickel-filtered CuK_α radiation on an Enraf-Nonius CAD-4 diffractometer. An ω-2θ scan at 1.8-10° min^{-1} over a range of (1.25 + 0.14 tan θ)° in ω (extended by 25% on each side for background measurement) was employed. Data were measured to 2θ = 150°. The intensities of three standard reflections, measured each hour of X-ray exposure time, remained constant to within 3%.

Of 3235 independent reflections measured and processed[23] 1967 had intensities greater than

$3\sigma(\underline{I})$ above background where $\sigma^2(\underline{I}) = \underline{S} + 2\underline{B} + (0.04\ (\underline{S}-\underline{B}))^2$ with $\underline{S}$ = scan count and $\underline{B}$ = normalized background count. Data were corrected for absorption, transmission factors ranging from 0.745 to 0.918. The structure was solved by direct methods in the centrosymmetric space group $\underline{P\bar{1}}$ which was indicated by the $\underline{E}$-statistics. The positions of the non-hydrogen atoms were determined from an $\underline{E}$-map and those of the hydrogen atoms from subsequent difference maps. The non-hydrogen atoms were refined with anisotropic thermal paramaters and the OH hydrogen with an isotropic thermal parameter. The remaining hydrogen atoms were fixed in idealized positions ($C(sp^2)$-H = 0.97, $C(sp^3)$-H = 0.98 Å). Neutral atom scattering factors were taken from ref. 24. The weighting scheme, $\underline{w} = 1/\sigma^2(\underline{F})$, gave uniform average values of $\underline{w}(|\underline{F}_o|-|\underline{F}_c|)^2$ over ranges of $|\underline{F}_o|$ and $\sin\theta/\lambda$ and was employed in the final stages of full-matrix refinement. Convergence was reached at $\underline{R} = 0.100$ and $\underline{R}_w = 0.126$ for 1967 reflections with $\underline{I} \geq 3\sigma(\underline{I})$.[25] The function minimized was $\sum \underline{w}(|\underline{F}_o|-|\underline{F}_c|)^2$, $\underline{R} = \sum||\underline{F}_o|-|\underline{F}_c|| \ / \ \sum|\underline{F}_o|$, $\underline{R}_w = (\sum \underline{w}(|\underline{F}_o|-|\underline{F}_c|)^2 \ / \ \sum \underline{w}|\underline{F}_o|^2)^{\frac{1}{2}}$.

On the final cycle of refinement the mean and maximum parameter shifts corresponded to 0.009 and 0.12σ, respectively. The mean error in an observation of unit weight was 2.39. A final difference map showed no unusual features. The final positional and isotropic thermal parameters ($\underline{U}_{eq}$ = 1/3 trace diagonalized $\underline{U}$) are given in Table 2. Bond lengths, bond angles, and intra-annular torsion angles appear in Tables 3-5, respectively. Calculated hydrogen parameters, anisotropic thermal parameters, torsion angles, and structure factors (Tables S1-S4) are included as supplementary data.[26]

Table 2. Final positional (fractional x 10^4, H x 10^3) and isotropic thermal parameters ($\underline{U}$ x 10^3 Å^2) with estimated standard deviations in parentheses

Atom	x	y	z	U_{eq}/U_{iso}
O(1)	-688(3)	5089(3)	7870(6)	68
O(2)	5207(4)	784(3)	7025(7)	90
O(3)	4107(4)	1249(3)	4227(7)	81
C(1)	2333(4)	3018(3)	6516(7)	47
C(2)	1651(4)	4218(4)	7012(7)	53
C(3)	212(5)	4248(4)	7761(7)	53
C(4)	-533(5)	2838(5)	6454(9)	75
C(5)	-362(7)	1586(5)	6407(10)	91
C(6)	1100(7)	921(5)	6239(11)	92
C(7)	1693(5)	1123(4)	7994(10)	73
C(8)	1496(5)	2330(4)	8272(8)	62
C(9)	90(5)	3046(4)	8283(7)	57
C(10)	3792(5)	2644(4)	6537(9)	64
C(11)	4586(5)	3477(4)	5149(12)	79
C(12)	6008(6)	3092(6)	5416(16)	126
C(13)	4400(7)	3715(6)	2793(14)	118
C(14)	-835(7)	2899(6)	10474(9)	102
C(15)	2314(7)	301(5)	9351(11)	102
C(16)	4409(5)	1469(4)	5776(11)	72
H(O)	618(9)	12(8)	650(17)	232(41)

Table 3. Bond lengths (Å) with estimated standard deviations in parentheses

Bond	Length(Å)	Bond	Length(Å)
O(1)-C(3)	1.206(5)	C(7)-C(6)	1.477(8)
O(2)-C(16)	1.306(6)	C(7)-C(15)	1.328(7)
O(3)-C(16)	1.190(6)	C(6)-C(5)	1.545(9)
C(3)-C(2)	1.519(6)	C(5)-C(4)	1.523(8)
C(3)-C(9)	1.515(6)	C(4)-C(9)	1.542(6)
C(2)-C(1)	1.521(6)	C(9)-C(14)	1.551(7)
C(1)-C(8)	1.578(6)	C(10)-C(16)	1.543(7)
C(1)-C(10)	1.507(6)	C(10)-C(11)	1.572(7)
C(8)-C(7)	1.494(7)	C(11)-C(12)	1.502(8)
C(8)-C(9)	1.519(7)	C(11)-C(13)	1.511(9)
O(2)-H(0)	1.16(10)		

Table 4. Bond angles (deg.) with estimated standard deviations in parentheses

Bonds	Angle(deg.)	Bonds	Angle(deg.)
O(1)-C(3)-C(2)	125.7(4)	C(3)-C(9)-C(8)	104.3(4)
O(1)-C(3)-C(9)	125.7(4)	C(3)-C(9)-C(4)	106.7(4)
C(2)-C(3)-C(9)	108.6(4)	C(3)-C(9)-C(14)	110.4(4)
C(3)-C(2)-C(1)	105.7(4)	C(8)-C(9)-C(4)	112.3(4)
C(2)-C(1)-C(8)	101.0(4)	C(8)-C(9)-C(14)	114.3(4)
C(2)-C(1)-C(10)	115.7(3)	C(4)-C(9)-C(14)	108.5(4)
C(8)-C(1)-C(10)	115.2(4)	C(1)-C(10)-C(16)	111.5(4)
C(1)-C(8)-C(7)	116.6(4)	C(1)-C(10)-C(11)	115.0(4)
C(1)-C(8)-C(9)	104.0(4)	C(16)-C(10)-C(11)	108.2(4)
C(7)-C(8)-C(9)	114.2(4)	O(2)-C(16)-O(3)	126.3(5)
C(8)-C(7)-C(6)	116.3(5)	O(2)-C(16)-C(10)	113.6(5)
C(8)-C(7)-C(15)	120.2(6)	O(3)-C(16)-C(10)	120.1(5)
C(6)-C(7)-C(15)	123.4(5)	C(10)-C(11)-C(12)	111.5(5)
C(7)-C(6)-C(5)	110.8(5)	C(10)-C(11)-C(13)	112.8(5)
C(6)-C(5)-C(4)	111.3(4)	C(12)-C(11)-C(13)	112.7(6)
C(5)-C(4)-C(9)	112.1(5)	C(16)-O(2)-H(0)	128(5)

Table 5. Intra-annular torsional angles (deg.) with standard deviations in parentheses

Atoms	Value(deg.)
C(9)-C(8)-C(7)-C(6)	47.1(7)
C(8)-C(7)-C(6)-C(5)	-50.8(6)
C(7)-C(6)-C(5)-C(4)	54.3(6)
C(6)-C(5)-C(4)-C(9)	-54.9(7)
C(5)-C(4)-C(9)-C(8)	50.1(6)
C(7)-C(8)-C(9)-C(4)	-45.1(6)
C(9)-C(3)-C(2)-C(1)	14.7(5)
C(3)-C(2)-C(1)-C(8)	-33.3(4)
C(2)-C(1)-C(8)-C(9)	40.7(4)
C(1)-C(8)-C(9)-C(3)	-32.0(4)
C(2)-C(3)-C(9)-C(8)	11.3(5)

Preparation of the bicyclic acid 22. A stirred solution of the keto acid 20 (40 mg, 0.15 mmol) and dry hydrazine (48 μL, 1.5 mmol) in 0.3 mL of diethylene glycol was heated at 110°C for 3 h. The mixture was then heated at ~190°C for 30 min, during which time excess hydrazine and water were distilled from the mixture. After the solution had been cooled to room temperature, 43 mg (0.75 mmol) of KOH was added and the mixture was heated at 190°C for 6 h. The solution was cooled, diluted with water (5 mL), acidified (1N hydrochloric acid), and extracted with ether (3 x 5 mL). The combined extract was dried ($MgSO_4$) and concentrated. The residual white

solid was purified by column chromatography (8 g silica gel, 1:4 ether-petroleum ether) and distillation (108-112°C/0.3 Torr) to provide 34 mg (90%) of the acid **22**, which exhibited m.p. 120-121°C (from ether-petroleum ether); IR ($CHCl_3$) 3500-2500 (br), 1703, 1644, 1390, 1374, 894 cm^{-1}; ^1H NMR (400 MHz) δ 0.96, 0.97 (d, d, 3H each, J = 7 Hz), 0.94 (s, 3H), 1.16-1.24 (m, 1H), 1.35-1.66 (m, 6H), 1.86 (br d, 1H, J = 10.5 Hz), 1.90-2.07 (m, 3H), 2.10 (dd, 1H, J = 9.5, 5 Hz), 2.13-2.24 (m, 1H), 2.46-2.58 (m, 1H), 4.67 (br s, 2H). Decoupling experiment: irradiation at δ 2.50 caused the signal at δ 1.86 to collapse to a s, the signal at δ 2.10 to collapse to a d (J = 5 Hz), and the resonances at δ 1.35-1.66 and 1.90-2.07 to simplify. Exact Mass calcd. for $C_{16}H_{26}O_2$: 250.1934; found: 250.1934.

Preparation of the bicyclic acid **23**. This material was prepared from the keto acid **21** via a procedure identical with that described above. From 30 mg (0.11 mmol) of **21** there was obtained 25.6 mg (90%) of **23** as a clear, colorless oil (distillation temperature 105-110 °C/0.3 Torr) that exhibited IR (neat) 3500-2500 (br), 1702, 1645, 1390, 1375, 895 cm^{-1}; ^1H NMR (400 MHz) δ 0.93, 0.94 (d, d, 3H each, J = 7 Hz), 0.95 (s, 3H), 1.16-1.22 (m, 1H), 1.34-1.55 (m, 4H), 1.57-1.66 (m, 1H), 1.79-1.90 (m, 2H), 1.91 (partially obscured br d, 1H, J = 11 Hz), 1.96-2.08 (partially obscured m, 1H), 2.05-2.15 (m, 2H), 2.18 (dd, 1H, J = 9, 5 Hz), 2.40-2.50 (m, 1H), 4.74 (br s, 1H), 4.80 (t, 1H, J = 2 Hz). Decoupling experiments: irradiation at δ 0.93 caused the signal at δ 1.96-2.08 to collapse to a d (J = 9 Hz); irradiation at δ 2.18 simplified the resonances at δ 2.40-2.50 and 1.96-2.08; irradiation at δ 2.45 caused the signals at δ 1.91 and 2.18 to collapse to a s and a d (J = 9 Hz), respectively. Exact Mass calcd. for $C_{16}H_{26}O_2$: 250.1934; found: 250.1931.

Preparation of the carbamate **26**. To a stirred solution of the acid **22** (46 mg, 0.185 mmol) in 1.5 mL of dry toluene (argon atmosphere) was added 64 μL (0.74 mmol) of oxalyl chloride and the mixture was stirred at room temperature for 45 min. The solvent and excess oxalyl chloride were removed under reduced pressure to afford the acid chloride **24** [IR (neat) 1794, 894 cm^{-1}] as a pale yellow oil. A solution of this material in dry acetone (1 mL) was added to a rapidly stirred solution of sodium azide (50.5 mg, 0.74 mmol) in 0.2 mL of water at 0°C and, after 15 min, 10 mL of hexanes and 5 mL of water were added. The layers were separated and the aqueous phase was extracted with hexanes (3 mL). The combined organic extract was dried ($MgSO_4$) and concentrated to provide the acyl azide **25** [IR (neat) 2130, 1714, 892 cm^{-1}] as a colorless oil. A solution of the latter substance in 0.2 mL of toluene was heated with stirring (argon atmosphere) for 2 h at 80°C. 2-Trimethylsilylethanol (80 μL, 0.55 mmol) was added and stirring at 80°C was continued for 20 h. The solvent and excess 2-trimethylsilylethanol were removed under reduced pressure and the residual material was dissolved in ether. The solution was washed with 5 mL of 1N aqueous NaOH and then was dried ($MgSO_4$). Removal of the solvent, followed by column chromatography (6 g silica gel, 1:6 ether-petroleum ether) of the crude product and distillation (125-130°C/0.3 Torr) of the material thus obtained, gave 60 mg (89%) of the carbamate **26**, which exhibited m.p. 79.5-80.5°C (from petroleum ether); IR ($CHCl_3$) 3446, 1709, 1644, 1465, 896 cm^{-1}; ^1H NMR (400 Mz) δ 0.05 (s, 9H), 0.73, 0.87 (d, d, 3H each, J = 7 Hz), 0.91 (s, 3H), 0.97 (t, 2H, J = 8.5 Hz), 1.13-1.23 (m, 1H), 1.36-1.51 (m, 5H), 1.59-1.68 (m, 1H), 1.77-1.88 (m, 1H), 1.90-2.00 (m, 2H), 2.00-2.16 (m, 2H), 2.20-2.31 (m, 1H), 3.47 (td, 1H, J = 10, 4 Hz), 4.06-4.20 (m, 2H), 4.31 (br d, 1H, J = 10 Hz), 4.65, 4.73 (br s, br s, 1H each). Decoupling experiments: irradiation at δ 4.11 caused the triplet at δ 0.97 to collapse to a s; irradiation at δ 0.73 caused the multiplet at δ 1.77-1.88 to simplify; irradiation at δ 1.80 caused the resonances at δ 3.47, 0.73, and 0.87 to collapse to a t (J = 10 Hz), a s, and a s, respectively; irradiation at δ 3.47 collapsed the multiplet at δ 1.77-1.88 to a septet (J = 7 Hz), the doublet at δ 4.31 to a s, and simplified the multiplet at δ 2.20-2.31; irradiation at δ 4.31 collapsed the signal at δ 3.47 to a dd (J = 10, 4 Hz). Exact Mass calcd. for $C_{21}H_{39}NOSi$: 365.2752; found: 365.2742.

Preparation of the carbamate **28**. This substance was made from the acid **23** via a procedure identical with that described above. From 25 mg (0.1 mmol) of **23** there was obtained 30 mg

(82%) of the carbamate **28**, which exhibited m.p. 86-87°C (from petroleum ether); IR (CCl_4) 3450, 1726, 1643, 1464, 904 cm^{-1}; ^1H NMR (400 MHz) δ 0.05 (s, 9H), 0.85, 0.88 (dd, 3H each, J = 7 Hz), 0.95 (s, 3H), 0.99 (t, 2H, J = 8.5 Hz), 1.17-1.24 (m, 1H), 1.29-1.55 (series of m, 5H), 1.59-1.74 (m, 2H), 1.75-1.95 (m, 2H), 1.99-2.16 (m, 2H), 2.25-2.36 (m, 1H), 3.41 (ddd, 1H, J = 10.5, 7, 4 Hz), 4.16 (t, 2H, J = 8.5 Hz), 4.43 (br d, 1H, J = 10.5 Hz), 4.77, 4.88 (br s, br s, 1H each). Decoupling experiments: irradiation at δ 2.30 caused the multiplet at δ 3.41 to collapse to a dd (J = 10.5, 7 Hz) and the signal at δ 1.76-1.95 to simplify; irradiation at δ 4.16 collapsed the triplet at δ 0.99 to a s; irradiation at δ 0.85 caused part of the multiplet at δ 1.59-1.74 to simplify; irradiation at δ 3.41 caused the signals at δ 4.43 and 2.25-2.36 to collapse to a br s and a td (J = 11, 5.5 Hz), respectively, and the signal at δ 1.59-1.74 to simplify. Exact Mass calcd. for $C_{21}H_{39}NOSi$: 365.2752; found: 365.2754.

Preparation of the amine **27**. A solution of the carbamate **26** (43.9 mg, 0.12 mmol) in 1 mL of dry THF was added to a stirred solution of n-Bu_4NF (136.5 mg, 0.5 mmol) in 0.5 mL of dry THF (argon atmosphere) and the mixture was heated at 50°C for 35 min. After the solvent had been removed (reduced pressure) from the cooled reaction mixture, pentane (5 mL) and water (4 mL) were added to the residue and the mixture was stirred vigorously for 10 min. The aqueous layer was separated and extracted twice with pentane. The combined organic extract was washed with brine and dried ($MgSO_4$). Removal of the solvent and distillation (70-75°C/0.3 Torr) of the residual material gave 18 mg (72%) of the amine **27** as a colorless oil that exhibited IR (neat) 3397, 3338, 1641, 889 cm^{-1}; ^1H NMR (400 MHz) δ 0.82, 0.92 (d, d, 3H each, J = 6.5 Hz), 0.94 (s, 3H), 1.14-1.22 (br d, 1H), 1.20-1.35 (br s, 2H), 1.32-1.60 (series of m, 5H), 1.61-1.70 (m, 1H), 1.70-1.83 (m, 1H), 1.83-1.93 (m, 1H), 1.97 (d, 1H, J = 10 Hz), 2.05-2.30 (m, 3H), 2.51 (dd, 1H, J = 8.5, 3.5 Hz), 4.77 (br s, 2H). Decoupling experiments: irradiation at δ 2.51 caused the multiplet at δ 1.70-1.83 to collapse to a septet (J = 6.5 Hz) and the multiplet at δ 2.05-2.30 to simplify; irradiation at δ 0.82 caused the multiplet at δ 1.70-1.83 to simplify. Exact Mass calcd. for $C_{15}H_{27}N$: 221.2145; found: 221.2142.

Preparation of the amine **29**. This material was prepared from the carbamate **28** via a procedure identical with that described above. From 26.9 mg (0.074 mmol) of **28** there was obtained 12 mg (73%) of the amine **29** as a colorless oil that exhibited IR (neat) 3387, 3307, 1643, 890 cm^{-1}; ^1H NMR (400 MHz) δ 0.86, 0.89 (d, d, 3H each, J = 6.5 Hz), 0.97 (s, 3H), 1.17-1.24 (br d, 1H), 1.30-1.80 (series of m, 10H), 1.95 (br d, 1H, J = 11 Hz); 2.02-2.15 (m, 2H), 2.23-2.34 (m, 1H), 2.34 (dd, 1H, J = 6.5, 3 Hz), 4.62, 4.75 (br s, br s, 1H each). Exact Mass calcd. for $C_{15}H_{27}N$: 221.2145; found: 221.2140.

(±)-Axamide-1 (**1**). To a stirred solution of the amine **27** (17.7 mg, 0.08 mmol) in 0.6 mL of dry ether (argon atmosphere) was added acetic formic anhydride (24 μL, 0.16 mmol) and the mixture was stirred at room temperature for 10 h. Ether (5 mL) and water (2 mL) were were added and the layers were separated. The aqueous phase was extracted twice with ether. The combined organic extract was dried ($MgSO_4$) and concentrated. Column chromatography (5 g silica gel, 1:6 ether-petroleum ether) of the residue and distillation (110-115°C/0.3 Torr) of the material thus obtained provided 18 mg (90%) of (±)-axamide (**1**) as a colorless oil that exhibited IR (neat) 3268, 1660, 890 cm^{-1}; ^1H NMR (400 MHz) δ 0.79, 0.89 (d, d, 3.6H total, cis rotamer, J = 7 Hz), 0.80, 0.88 (d, d, 2.4H total, trans rotamer, J = 7 Hz), 0.92 (s, 1.8H, cis rotamer), 0.94 (s, 1.2H, trans rotamer), 1.14-1.27 (m, 1H), 1.30-1.57 (m, 5H), 1.58-1.69 (m, 1H), 1.81-2.18 (m, 5H), 2.24 (qd, 0.6H, cis rotamer, J = 10, 5 Hz), 2.31-2.42 (m, 0.4H, trans rotamer), 2.96 (ddd, 0.4H, trans rotamer, J = 12, 8.5, 4 Hz), 3.91 (td, 0.6H, cis rotamer, J = 10, 4 Hz), 4.65, 4.82 (br s, t, 0.4H each, trans rotamer, J = 2 Hz), 4.68, 4.75 (t, t, 0.6H each, cis rotamer, J = 2.5, 2.0 Hz), 5.18 (br d, 0.6H, cis rotamer, J = 10 Hz), 5.38 (br t, 0.4H, trans rotamer, J = 12 Hz), 7.90 (d, 0.4H, trans rotamer, J = 12 Hz), 8.15 (d, 0.6H, cis rotamer, J = 2 Hz). Exact Mass calcd. for $C_{16}H_{27}NO$: 249.2094; found: 249.2091.

(±)-10-epi-Axamide-1 (**8**). This compound was obtained from the amine **29** via a procedure identical with that described above. From 12 mg (0.054 mmol) of **29** there was obtained 11.8 mg

(88%) of (±)-8 as a viscous, colorless oil that exhibited IR (neat) 3288, 1659, 896 cm^{-1}; ^1H NMR (400 MHz) δ 0.84-0.98 (unresolved doublets and singlets due to 2 rotamers, 9H total), 1.17-1.79 (m, 8H), 1.79-1.94 (m, 2H), 1.96-2.10 (m, 1H), 2.10-2.19(m, 1H), 2.30-2.46 (m, 1H), 2.94 (ddd, 0.5H, J = 11, 8, 3 Hz), 3.84 (ddd, 0.5H, J = 11, 7, 3 Hz), 4.59, 4.76 (br s, br s, 0.5H each), 4.79-4.84 (m, 1H), 5.25 (br d, 0.5 H, J = 11 Hz), 5.42 (br t, 0.5H, J = 11 Hz), 7.97 (d, 0.5H, J = 11 Hz), 8.31 (br s, 0.5H). Exact Mass calcd. for $C_{16}H_{27}NO$: 249.2094; found: 249.2092.

(±)-Axisonitrile-1 (2). To a stirred solution of (±)-axamide-1 (1) (12.5 mg, 0.05 mmol) in 0.8 mL of dry pyridine (argon atmosphere) was added solid p-TsCl (29.5 mg, 0.15 mmol) and the mixture was stirred at room temperature for 3 h. A few chips of ice were added and the mixture was poured into ice-cold water. The mixture was extracted with pentane (2 x 5 mL). The combined extract was washed twice with cold water, dried ($MgSO_4$), and concentrated. Column chromatography (3 g silica gel, 1:14 ether-petroleum ether) of the residue and distillation (65-70°C/0.3 Torr) of the material thus obtained provided 10 mg (86%) of (±)-axisonitrile-1 (2) as a white solid that exhibited m.p. 45-46°C (from petroleum ether); IR (CCl_4) 2136, 1645, 1390, 1375, 899 cm^{-1}; ^1H NMR (400 MHz) δ 0.88, 1.02 (d, d, 3H each, J = 6.5 Hz), 0.99 (s, 3H), 1.19-1.29 (m, 1H), 1.40-1.59 (m, 5H), 1.59-1.71 (m, 1H), 1.94-2.13 (m, 3H), 2.14-2.23 (m, 2H), 2.47 (m, 1H), 3.23 (tt, 1H, J = 7.5, 1.5 Hz), 4.79-4.85 (m, 2H). Decoupling experiment: irradiation at δ 2.47 caused the signal at δ 3.23 to collapse to a br d (J = 7.5 Hz) and the multiplets at δ 2.14-2.23 and 1.94-2.13 to simplify. ^{13}C NMR (75 MHz, proton decoupled) δ 19.068, 19.779, 24.371, 24.442, 27.719, 29.727, 31.279, 33.301, 39.638, 40.092, 45.167, 57.137, (67.691, 67.763, 67.724, triplet), 111.633, 148.299, (155.535, 155.621, 155.689, triplet). Exact Mass calcd. for $C_{16}H_{25}N$: 231.1989; found: 231.1993. The spectral data derived from the synthetic material were identical with those of an authentic sample of (+)-axisonitrile-1.[21]

(±)-10-epi-Axisonitrile-1 (9). This substance was derived from (±)-10-epi-axamide-1 (8) via a procedure identical with that described above. From 8.9 mg (0.036 mmol) of (±)-8 there was obtained 7.2 mg (87%) of (±)-9, which exhibited m.p. 53-54°C (from petroleum ether); IR (CCl_4) 2135, 1644, 1391, 1377, 901 cm^{-1}; ^1H NMR (400 MHz) δ 0.92, 1.04 (d, d, 3H each, J = 7 Hz), 1.00 (s, 3H), 1.21-1.32 (m, 1H), 1.38-1.59 (m, 4H), 1.59-1.75 (m, 2H), 1.75-1.92 (m, 2H), 1.92-2.02 (m, 1H), 2.05 (d, 1H, J = 11 Hz), 2.14 (br d, 1H, J = 14 Hz), 2.22-2.34 (m, 1H), 3.18-3.25 (m, 1H), 4.72 (t, 1H, J = 2 Hz), 4.80 (t, 1H, J = 2 Hz). Decoupling experiment: irradiation at δ 2.28 caused the multiplet at δ 3.18-3.25 to collapse to a br d (J = 8 Hz), the doublet at δ 2.05 to collapse to a br s, and the multiplet at δ 1.75-1.92 to simplify. ^{13}C NMR (75 MHz, proton decoupled) δ 19.423, 19.510, 22.941, 23.786, 24.621, 30.457, 31.406, 33.156, 39.995, 41.974, 43.175, 57.922, (63.912, 63.973, 64.046, triplet), 111.392, 146.862, (155.026, 155.097, 155.168, triplet). Exact Mass calcd. for $C_{16}H_{25}N$: 231.1989; found: 231.1981.

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